REMARKS

The present amendment is filed in response to the Office Action dated June 16, 2006. Claims 1-10, 14-26, 28, 31-44, 46-61 are now present in this case. Claims 56-61 were withdrawn as being directed to a non-elected invention.

The Examiner stated that the affidavit under 37 C.F.R. § 1.132 filed February 24, 2006 is insufficient to overcome the rejection of claims based upon 35 U.S.C. § 112, first paragraph, as set forth in the last Office Action because Dr. Shawn Iadonato is of extraordinary skill in the art (affidavit, points 1, 2, and 3) and for other reasons as follows:

a. The affidavit allegedly did not establish when the disclosed procedures and experimentation were performed, and therefore did not demonstrate that the claimed invention was enabled at the time of filing in the instant application.

b. The disclosed procedures and experimentation in the affidavit required the use of a URU population (affidavit, page 2, point 7, line 2). Independent claims 1, 20 and 41 do not recite any requirement for the use of a URU population.

c. The claims are broad in that they are drawn to identifying a drug target associated with a disease, without any limitation to what disease is targeted. The affidavit allegedly supports only the identification of a drug target for hepatitis C.

A new affidavit of Dr. Shawn Iadonato is submitted herewith as discussed below in reference to the rejection under 35 U.S.C. § 112. To further address the ground of rejection, applicants submit herewith the affidavits under 37 C.F.R. § 1.132 of Dr. Cammie Lesser and Dr. Richard Myers

Dr. Lesser attests that she has read the patent specification, and concludes that undue experimentation would not be required to practice the invention. In paragraph 9 of the affidavit, Dr. Lesser states that application provides a "very effective short-cut to drug target discovery". In paragraph 10, Dr. Lesser attests that the methods of the application are distinguished from current methods of target and drug discovery.

Dr. Lesser is a member of the large class of physicians and scientists who will benefit from the invention. She is not an inventor, nor is she employed by the assignee in any capacity. Her knowledge comes solely from arms-length review of the

specification. Applicants submit that Dr. Lesser's testimony fully addresses and overcomes the rejection.

Dr. Myers serves on the Scientific Advisory Board of the applicants' company, Illumigen Biosciences, Inc. However, Dr. Myers' statements are based on his independent work beyond his service to Illumigen. First, Dr. Myers serves as Chairman of the Department of Genetics, Stanford University School of Medicine, and holds other professional positions as provided in paragraph 1 of his affidavit, and his Curriculum Vitae. Secondly, Dr. Myers is uniquely qualified to attest to the amount of experimentation expected to be involved in practicing the invention, in view of his extensive service on NIH Study Sections that review grant proposals. This is discussed in paragraph 4 of his affidavit. Thirdly, Dr. Myers works closely with physicians and epidemiologists to study the genetic basis of human disease. He understands the procedures for identifying matched individuals, for example in the context of the ARA and ARU populations of the present methods. These and other related points are discussed in detail in paragraph 7 of Dr. Myers' affidavit.

Claims 1-19, 47, 49, 50, and 51 were rejected under 35 U.S.C. § 101 because the claimed invention allegedly is directed to non-statutory subject matter. According to the Examiner, these claims recite a computer implemented method involving the classification of medical data of populations and the identification of a drug target. Though the properties calculated by the model are physical properties, the data is nonetheless generated within a computer without a physical manifestation such as the transfer of data between a memory and a processor, a physical step such as obtaining of a sample or, the visual display of results.

The Examiner kindly provided a suggestion for making the method steps statutory, and accordingly the claims have been amended to include a step of displaying the data for a user. The amendment is supported in the application, for example at page 17, lines 1-3, and no new matter is added. Reconsideration and withdrawal of the rejection are respectfully requested.

Prior to addressing the remaining ground of rejection, applicants wish to review the invention and point out the new features of the claimed method. To further clarify the distinctions between "traditional" drug discovery and applicants' invention, it is

important to clarify what is meant by "screening" in the context of traditional discovery, and to distinguish it from screening as performed in the methods of the invention. Traditional "screening" of targets could include (a) biochemical testing of numerous proteins to determine which proteins correlate with a disease or condition. Next, (b) the pathways that the proteins belong to would be identified. After that, (c) protein-protein or protein-antibody interactions would be studied. Then, (d) a drug or protein therapeutic would be tested in an animal model of the disease. If the treatment was not effective, then other targets would be studied, with a return to step (a). If the treatment was effective, two more hurdles had to be overcome: (e) were there unacceptable side effects, and (f) did the animal results apply when the treatment was tested in humans? In respect to this method, applicants agree with the Examiner's conclusion that thousands of targets might have to be studied.

Applicants' claimed method, in short, avoids steps (a)-(f) and provides a shortcut by identifying a model in humans of what the therapeutic strategy should be. The ARU individuals are the end-point of the traditional drug discovery methods, because they represent humans in which a disease or condition is being treated or prevented, without side effects. The "screening" needed to achieve this is genetic study using high-speed sequencing and comparisons of many genes to focus rapidly on a much smaller set of several, or perhaps only one, differences between the affected and unaffected individuals.

Thus, the term "screening" has a different meaning here: it refers to the rapid computer-assisted comparison of sequences, and is not the traditional biochemical comparison of disease markers. That step may occur in the claimed method, but only if a few mutations have been identified by the computer-based screening.

Claims 1-10, 14-26, 28, 31-44 and 46-55 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner cited *In re Wands* (8 U.S.P.Q.2d 1400 (C.A.F.C. 1988)) for the eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

Applicants reiterate that the present application provides extensive guidance to allow one of ordinary skill in the art to obtain a target that is within the scope of the claims and by following the guidance, applicants have developed such a target and a drug. The Examiner's individual comments on these factors are reiterated below with the relevant page number in the Office Action, followed by applicants' remarks.

At page 6 of the Office Action, paragraphs (a) and (b), the Examiner states that the disclosure does not provide guidance as to identifying genetic variations between ARA and ARU subpopulations that result in the identification of a drug target for a given biological condition. On the contrary, the application does provide such guidance. As described by Dr. Richard Myers in paragraph 7 of his affidavit that accompanies this response, it is feasible and within ordinary skill in the art to identify such genetic variations. Dr. Myers provides examples of human diseases in which such variations have been identified, of which an inherited form of childhood epilepsy, hemochromatosis, and basal cell nevus syndrome, are a few. Dr. Myers also states that targets can be identified by following the claimed methods. For example, at paragraph 9 of his affidavit, Dr. Myers states that many drug targets are polypeptides, and in some cases the drug itself is a polypeptide. The Examiner provides no basis for saying that this would entail an unpredictable amount of experimentation. (Office Action at page 6, lines 3-4).

The points discussed above as (a) and (b), and the other factors listed as (c) through (h) at pages 6-7 of the Office Action, are discussed fully below. To facilitate review of applicants' points, applicants have reproduced the Examiner's separate statements ("Comments"), and respond to each one separately.

Comment 1 (Page 8, line 1). The application recites (page 10, line 26 to page 11, line 10) the use of PCR to amplify the coding regions of each candidate gene and then comparing each patient's candidate gene sample sequence to a reference sequence to identify all sequence mutations and variants. After taking the DNA samples, the process of isolating the coding region pertinent to the disease of interest is not described and thus applicants have not described how to identify where the genetic variation associated with the disease exists. The claimed invention does not include prior knowledge of where to look for the coding region of interest and the claim is broader than applicants own example which includes locating a target gene for hepatitis C (Remarks, page 28, 3 paragraph; and page 30, 2nd paragraph). Studies of hepatitis C exist which predate the instant applications. However, the genetic basis far many disease have not been studied and can not provide guidance of where on the genetic code the mutations of interest would exist. Without prior knowledge, finding the difference for two populations, as pertaining to a specific genetic trait requires vast undue experimentation and is not enabled in the instant application.

Response: An element of the present invention is that prior knowledge of the genetic basis of a disease is not required. Applicants agree that hepatitis C has been extensively studied although not as well as other infections such as HIV. A crucial point of the claimed invention is that previously known methods (sample collection, DNA sequencing, sequence comparison) are applied in a new way. In the past, the disease itself was studied by analyzing the defective genes and proteins of people afflicted with the disease or condition. The novelty of the present invention is the use of ARU – at risk, unaffected – populations to discover the phenotype of people who are naturally resistant to the disease or condition. The difference that is found in the unaffected population becomes the basis of the treatment.

The revolutionary aspect of applicants' claimed invention can be illustrated with reference to published commentaries on the state of the art of medicine at the time the application was filed. Writing in Nature Biotechnology 14:1516-1518 (1996), Jurgen Drews (President of Global Research for Hoffmann-La Roche) stated that "companies that persist in the 'classic' approach to developing therapeutics – the screening of

chemical compounds for potential therapeutic effects on unknown targets – are almost certainly doomed to failure. (Page 1516, first paragraph.)

Applicants' new approach to target discovery is clearly not the "classic" approach under this definition. Drews continues, stating that target discovery did not depend on complete pre-knowledge of the relevant pathways. "These 417 targets were not discovered by knowing completely the pathways that were relevant in diseases." (Page 1516, third column, second full paragraph.) Furthermore, for some drugs currently sold, "nearly half the targets remain unknown." (Page 1518, first column, lines 8-10).

Writing in 1996, Drews envisioned the need for cross-company collaboration to conduct drug discovery using the new approaches he outlines in his article. "It will be necessary for the pharmaceutical company wishing to develop drugs rapidly from the Human Genome Project to form alliances with many partners – in both biotechnology and academia – to carry out this process as efficiently and as effectively as possible." (Page 1518, third column, last paragraph.) Despite Drews' predictions, the present applicants have developed a method of drug target discovery that does not require the massive collaboration envisioned by Drews. Furthermore, this discovery corroborates Drews' conclusion that successful target discovery, development, and treatment in humans does not require a priori knowledge of the coding region where the mutation exists. In fact, in some cases successful drugs affect an unknown target. This point is supported by Dr. Myers in his affidavit, particularly paragraphs 12 and 13.

Comment 2 (Pages 8-9). Applicants state (Remarks, page 27, lines 6-9) that the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain a polypeptide. This is not persuasive because a polypeptide is not a drug target. Furthermore, in the discussion of classification of populations, followed by PCR, then DNA sequence analysis, followed by detection of the mutation (specification, page 10, line 22 to page 11, line 25), it is not disclosed how the relevant polynucleotide is detected. Additionally, how the functional coding region carrying the genetic difference of interest is located and determination of whether it is a drug target is not described.

Remarks: Applicants fail to understand the statement that "a polypeptide is not a drug target." If a polypeptide or protein plays a crucial role in a disease process or a reaction to infection by a virus, it is the target, whether the treatment is an antibody, a small molecule, more of the same polypeptide, or antisense to prevent expression of the polypeptide.

The "relevant polynucleotide" is detected by virtue of the mutation being within that sequence. The genetic difference of interest need not be in a coding region: it could be in a regulatory region, such as an upstream promoter. One of ordinary skill in the art will be able to run the appropriate analyses to identify whether the mutation is in a coding or non-coding region. As stated by Dr. Myers in his affidavit, paragraph 9, "entire classes of important drugs" act on polypeptide drug targets, and in some diseases the polypeptide itself is the drug.

In his article in Nature Biotechnology, cited above, Jurgen Drews states that there are 417 receptors, enzymes, ion channels, and other targets of drug therapy (page 1516, Figure 1). On page 1518, first paragraph, Dr. Drews notes that receptors, enzymes, and growth factors, all of which are polypeptides, form the bulk of drug targets. Thus, in the majority of cases, the polypeptide is in fact a drug target.

Comment 3 (Page 9). Applicants state (Remarks, page 28, last paragraph) that Dr. Iadonato attests to the conclusion that when the guidance of the specification is followed, a target and drug are identified. This is not persuasive because the specification does not disclose specifically how to obtain the drug target, or for example how one determines which regions in the genome encode for the receptor that leads to a treatment.

Remarks: The drug target naturally flows from identification of the genetic differences. Where a genetic difference causes one at-risk group of individuals to be unaffected where another at-risk group of individuals is affected, then the bulk of the work has already been done by nature. All that is left is for the person of skill to identify the biological manifestation of the genetic difference, whether it is an increase, a decrease, or a change in the protein encoded by or regulated by the identified mutations. Without regard to the outcome of this last step, as soon as the target has been identified by the presence of mutations that associate with the ARU versus the

ARA group, then the claims of the present invention have been achieved. A separate step of determining which regions code for "the receptor that leads to a treatment" is not called for. Applicants fail to understand the relevance of this statement, as receptors form only one class of potential drug targets, and request that the Examiner clarify this point.

Comment 4 (Page 9). Applicants state (Remarks, page 29, lines 1-2) that working examples are provided on pages 30-34 of the specification. Upon examination, no working examples are found for the identification of a drug target. Pages 30-34 are further descriptions of how to collect and classify data of the populations. The section is titled "Individual Subject Analysis and Classification." Lines 14-16 of page 34 recite "the knowledge gained from this genetic analysis can also form the basis for diagnostic assay or vaccine development." However, specific examples of how one would use the genetic analysis to form a vaccine or identify a drug target are not taught.

Remarks. The identification of the biological difference between the ARA and ARU groups is the identification of the drug target. The mere fact that a functionally relevant biological difference between the ARA and ARU group is identified in a gene indicates that said gene is a drug target. This notion, that the biologically relevant difference directly identifies the drug target, would be appreciated by those skilled in the art. In support thereof, applicants refer to the affidavits of Dr. Richard Myers and Dr. Cammie Lesser. Dr. Myers states, at paragraph 10, that applicants provide methods for identifying mutations differentially associated with the ARA and ARU groups. Dr. Lesser states, at paragraph 6, that she, and anyone of ordinary skill in the art, would appreciate how the identification of functional genetic variations between the ARA and ARU groups "directly identifies the gene containing the genetic variations as a drug target." Thus, two experts possessing the ordinary skill that one would have for working in this area, attest to their understanding of how one would use the genetic analysis as claimed.

Comment 5 (Page 9). Applicants state (Remarks, page 31, 2nd paragraph) that the Examiner has provided no evidence that the claimed methods would be more difficult and unreliable than known methods.

The Examiner states that she did not allege that "claimed methods would be more difficult and unreliable than known methods." The Examiner also states that there is undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed. The specification provides descriptions for the collecting and scoring of data from the population to achieve the final classification of sub-populations in ARU, ARA, and URA. However, the details for identifying a drug target based on the classification are not described. Thus, there is not sufficient support to enable one skilled in the art to make or use the invention. The specification recites (page 13, lines 16-20), "As those skilled in the art can appreciate, this type of genotypic evaluation is significant within the present invention due to the classification of subjects into the phenotypic categories discussed above. That is, the discovery of genetic drug targets become a valuable tool when the ARU phenotype is compared against other sub-population." Though the statement points out the usefulness of the described classification method for the identification of drug targets, it does not specifically describe the invention as containing a method for identifying drug targets nor does it describe the method, experimental or computational, for identifying drug targets. The identification of a drug target requires the sorting out of 1000's of targets present in most organisms. Because the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete by someone skilled in the art, the general mention of the method in the specifications of the instant application does not provide sufficient guidance.

Remarks: Applicants focus on the Examiner's conclusion, "the identification of a drug target requires the sorting out of 1000s of targets present in most organisms." (Page 20, lines 14-15.) This statement is refuted by both Dr. Myers and Dr. Lesser. Dr. Myers states at paragraph 12 that the statement "is incongruous with the history of biomedical research." Dr. Lesser states at paragraph 8 that "few, if any, drug targets have been identified by 'sorting out of 1000's of targets present in most organisms.'"

In addition to the sworn statements of these experts, applicants call to the Examiner's attention statements made by Dr. Jurgen Drews, the President of Global Research for Hoffman-La Roche. As of 1996, 417 targets had been identified. Thus, thousands of targets were not "sorted out" to yield most of the drugs known today. In a more recent article, published in 2001, Dr. Thomas Bumol and Dr. August Watanabe, both of Lilly Research Laboratories, stated that there is the potential for 5,000 genes to be important targets or to produce therapeutic proteins. However, as of 2001, these authors continued to focus on a traditional route of drug discovery: a route that is successfully circumvented by applicants' novel approach to drug discovery.

Bumol and Watanabe outline the stages of target identification and validation, including "biochemistry, pharmacology, and medicinal chemistry" playing essential roles in identifying targets in the "posthuman genome" era. (Page 551, last paragraph.) In fact, applicants' methods eliminate the need for these steps in the *discovery* phase of target identification. For target validation, the authors suggest continued reliance on hypotheses based on animal models, such as leptin playing a role in obesity in mice. (Page 552, last paragraph.) Applicants' methods go straight to the human aspects of disease, and avoid the false starts and misleading information that often result from animal models.

Bumol and Watanabe discuss the use of "screening strategies to discover drug candidates that modulate the targets to test the therapeutic hypotheses." (Page 553, second column, first full paragraph.) In applicants' methods, the stage of therapeutic hypothesis is incorporated into the simultaneous discovery of the target and the therapy, as evidenced by the phenotype of the ARU population. Bumol and Watanabe also note the need for *in vivo* models during the preclinical (*i.e.* animal testing) phase before testing begins in humans. (Page 553, third column, lines 1-7). In contrast, by studying humans to begin with, applicants gain information about the effect of the potential drug in humans by studying the ARU populations.

Applicants very respectfully, but firmly, state that the entire point of the inventiveness of the claimed method is that no sorting out of thousands of targets is required. The target is identified because it is the difference between the ARU and ARA populations. Why would one need to look beyond the specific difference between these

two populations? Applicants request that the Examiner explain why "thousands" of targets would have to be sorted out, because this statement seems to represent a fundamental misunderstanding of the entire ARU and ARA comparison exercise in the first place. The invention circumvents the "years" cited by the Examiner by relying on the evidence provided by comparing the ARU and ARA groups for the key genetic difference. Furthermore, as the two cited articles (Drews; Bumol) note, even in 2001, just after the application was filed, there were not "thousands" of targets. There were at most 500 or so targets. This is the kind of information available in the art that the Examiner is expected to be familiar with, not broad-ranging generalizations that do not reflect the true state of the art.

In conclusion, evolution has sorted out the targets and provided the person skilled in the art with the end result of the treatment, in the form of the ARU phenotype.

Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, may be withdrawn in view of the arguments above which address the Examiner's specific statements about the claimed method, and in view of the affidavits under 37 C.F.R. § 1.132 of Dr. Cammie Lesser and Dr. Richard Myers

The Examiner objected to the affidavit of Dr. Shawn Iadonato on the grounds that he is of extraordinary skill in this art. To remedy that, applicants submit the affidavits of Dr. Lesser and Dr. Myers, as discussed above. Dr. Iadonato's new affidavit attests to the fact that the first time the claimed methods were applied to a study population, a mutation that correlated with resistance to Hepatitis C was discovered. The affidavit attests to the applicability of the claimed methods to identifying a mutation by comparing ARA and ARU populations. The Examiner has provided no grounds for limiting the claims to hepatitis C, because there is no evidence that the methods are not enabling for other disease states. To the extent that the previously submitted affidavit of Dr. Shawn Iadonato was deemed not to be persuasive, applicants submit that the presently filed affidavit overcomes those concerns.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Applicants thank the Examiner and acknowledge the withdrawal of the following rejections: the rejection of claims 1-10, 14-19 and 47-55 for being vague and indefinite in the Office Action mailed August 29, 2005; and the rejection of claims 1-10, 14-26, 28, 31-44, and 46-55 over the NIH's risk assessment models in the Office Action mailed August 29, 2005.

If fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258. A duplicate copy of this document is enclosed.

In view of the above amendments and remarks, the applicants respectfully request reconsideration and allowance of the application. If questions remain regarding the present application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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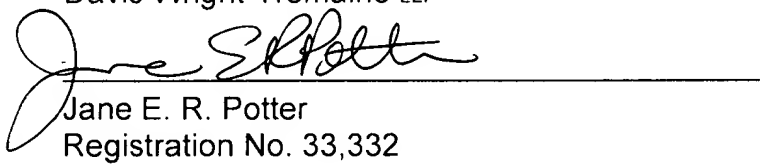

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